Cardiac arrhythmias and Griffiths phase: desynchronization of excitable cells

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Challenges of $\mathbb{C}$ arrhythmias raised by the data

- Most frequent cause of embolic stroke (AF), with evolution to chronic disease. Major cause of natural death (VF), about 5% only are saved.
- *Hysteresis*: strike twice and patient resuscitates.
- Most models refer to chaotic dynamics, but this does not describe *spontaneous* reversions to lesser $\mathbb{C}$ arrhythmias.

Figure 1 : Cardioversion forces reversion by applying electric shocks. A kind of hysteresis.

Some features suggest intrinsic *disorder*:

- The data show *intermittency* of beat-to-beat intervals and peaks amplitude.
- Slow evolution of vulnerability (the susceptibility), so called remodeling.

Conduction velocity is *not* known to be very much affected. Intermittency may instead reveal nucleation and contamination processes *à la* Pomeau. However, the medium is excitable and excitability is a robust cycle to any homo- or heteroclinic nucleation.

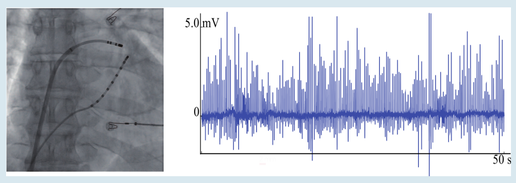


Figure 2 : (Left) Radiography of atria showing catheters. (Right) Turbulent like temporal series of a complex atrial arrhythmia.

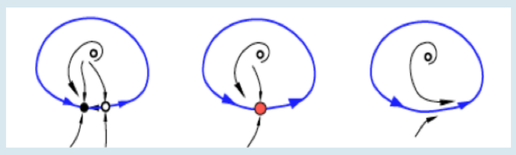


Figure 3 : Excitable cycles are immune to tangles. They can become oscillatory but not easily chaotic.

The probability distribution of amplitude increments shows scaling $p(A) \sim A^{-\tau}$, with seemingly non-universal Fisher exponents in the range $0.5 \lesssim \tau < 3$. Moreover, long range correlations are found *systematically*.

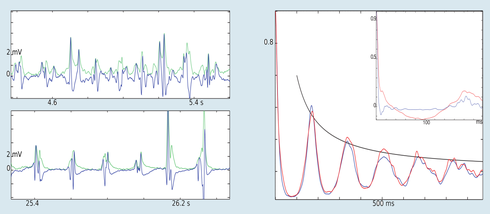


Figure 4 : (Left) Two consecutive instances in one patient of the signal trace, with an envelope estimation by Hilbert transform. (Right) Beat-to-beat long range correlations.

Alteration of conduction, e.g. on a nearly percolating fibrotic substrate, yields fancy anatomical reentries, but no such intermittent behavior. We believe that the data is suggestive of *fragmented* pulses, following from the *desynchronization* of the network of electrically coupled excitable cells.

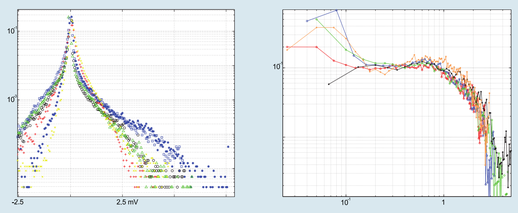
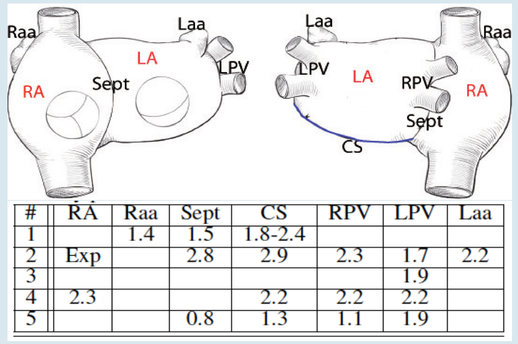


Figure 5 : (Left) Semi log plot of instances of the signal amplitude PDFs. (Right) Loglog plot of the collapse onto a universal scaling function, albeit for different Fisher exponents.



#	RA	Raa	Sept	CS	RPV	LPV	Laa
1		1.4	1.5	1.8-2.4			
2	Exp		2.8	2.9	2.3	1.7	2.2
3						1.9	
4	2.3			2.2	2.2	2.2	
5			0.8	1.3	1.1	1.9	

Figure 6 : Table of the measured Fisher exponents for 5 patients. It appears that regional gradients may indicate a source of activity.

The basic idea is that cycles become coupled to a *new d.o.f. inducing an effective beat-to-beat interaction*, i.e. *memory*, which induces intermittency .

The plausible physiology

- Memory can be a responsive sensitivity to left-overs after each pulse passage.
- Intermittency suggests some sort of *nucleation* process. For instance with a bistable cell cycle.
- The model introduces resonant interactions between cell cycles and inter-cell modulations. Temporal chaotic dynamics follow for two or three coupled cells, spatio-temporal intermittency for any greater number of cells.
- The coupling is induced by abnormal *gating polar asymmetries and sensitivities* of cardiac connexins.

An *unstable modulation* of the gap junction channel conductances is described. The argument is essentially as follows: above an instability, inter-cell cycles may locally saturate the connexins, which temporarily become *inhibitory*.

$$\begin{cases} \frac{\partial}{\partial t}U_m &= \mu U_m - \beta U_m^3 - J_m + D\Delta U_m - \vec{\nabla}\cdot(\tilde{g}\rho) \\ \frac{\partial}{\partial t}J_m &= \gamma U_m - \sigma J_m \\ \frac{\partial}{\partial t}\tilde{g} &= -\alpha\vec{\delta}\rho - \nu\tilde{g} \\ \frac{\partial}{\partial t}\rho &= -\tilde{g}\cdot\vec{\nabla}U_m - \nu_2\rho \end{cases} \quad (1)$$

where (U_m, J_m) are the membrane potential and membrane current of cells, (g, ρ) are the continuous gap junction conductance and density of abnormally opened channels. This model simply stipulates the *conservation of free and bound* charges. Parameters account for intrinsic properties. D is the resting conductivity, while $\tilde{g}$ encodes *fluctuations* of the directional conductance. There exists a *Rayleigh number*: $\mathcal{R}_a \equiv \frac{\alpha J_0}{D\nu\nu_2}$, where $J_0 \approx \langle\tilde{g}\rho\rangle$ is a forcing boundary current.

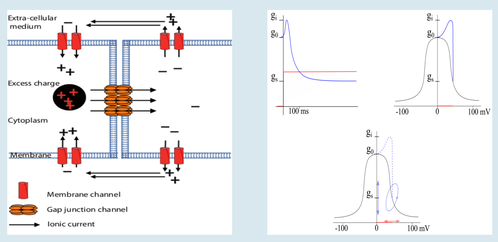


Figure 7 : (Left) Schematic drawing of gap junctional ionic exchanges, where the excess (Black) is due to bound charges. (Right) Schematic cycle of gap junction conductance induced by the instability.

For a few coupled cells only, chaotic dynamics are found. With spatial dimension, the system quickly bifurcates toward turbulent dynamics.

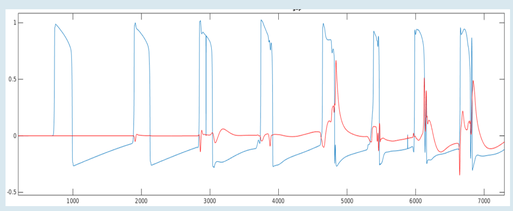


Figure 8 : Illustration of bound charges (red) inhibiting membrane currents, which process alters action potentials (blue).

Domain growth and signal analysis

- Gap junction channels have altered couplings with "turbulent" dynamics.
- *Back-scattering* is normally protected by chirality and refractory period. Occurrences are like abnormal excitations (with continued pulses) or micro-reentries (with discontinued pulses). Random annihilation and re-emission give a hierarchical structure of propagation in 1+1D. Pulses in 2D roughen and split.
- Write $\Psi = U_m + iJ_m = Ae^{i\theta}$. Necessary symmetry breaking terms are $\frac{i}{2}\left(\zeta\Psi^{*2} + \alpha\Psi^* - c.c.\right)$: Back-scattering is described at an *Ising-Bloch transition* (no phase-phase transition).
- "Bare" invariance $\Psi \to \Psi e^{i\varphi}$ of topological solutions, promoted to gauge $(\alpha, \zeta) \mapsto \left(-i\alpha e^{i\varphi}, -i\zeta e^{2i\varphi}\right)$: $\pi/2$ rotates internal dynamics from excitable (Fitzhugh-Nagumo) to oscillatory ($\mathbb{C}$GL). Anything in between with equilibrium locally modified $\theta_{eq} \to \theta_{eq} + \varphi(\mathbf{x})$. The phase model describes *charge density waves*: $\partial_t\theta = D\Delta\theta - H\sin\left(\theta + \varphi\left(\mathbf{x}\right)\right) + F$
- The phenomenology should be that of *depinning* directed fronts on a disordered medium. Since disorder is turbulent (heavy-tail PDFs, $k^{-\alpha}$ spectra), the rare-events dominated **KPZ** fixed point may well describe the dynamics *multi-scaling*.

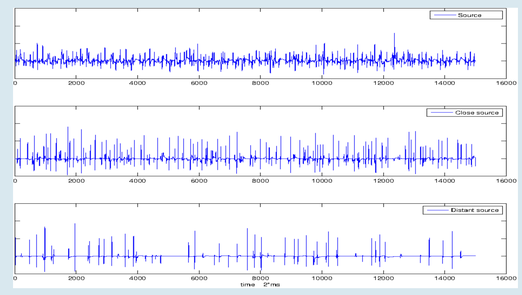


Figure 9 : Instance of three traces of the gap junction flux divergence near, at mid distance, and far from the boundary source. Fisher exponents decrease gradually with the distance from the source.

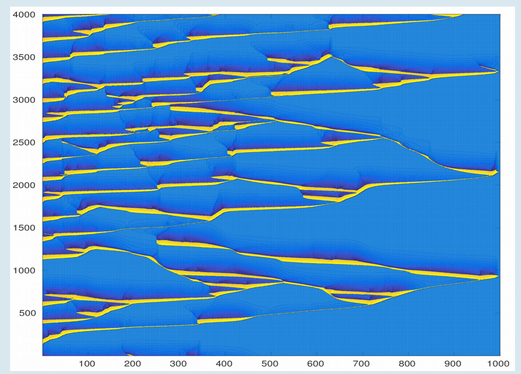


Figure 10 : Spatio-temporal map of the membrane potential showing many back-scattering events, some abnormal automaticity, and an overall hierarchical branching propagation.

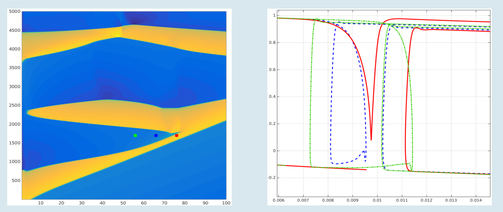


Figure 11 : An Ising-Bloch transition associated with a back-scattering event. (Right) Phase portrait(J_m, U_m) at three different points.

- Rare events are related to the **U**(1) defects. How do these appear in the recorded time series?
- The hierarchical dynamics creates a fractal signal. Rare-events tend to favor multi-fractal signals.
- Singularity analysis is crucial.
- Optimization/probabilistic methods needed to decode the *sparsity* of meaningful events.

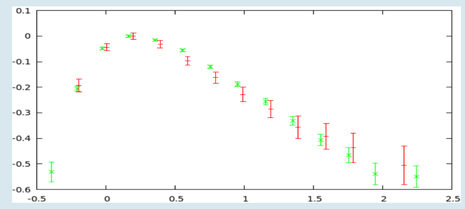


Figure 12 : Singularity spectrum of one experimental and one numerical time series, with equal Fisher exponents. The spectrum shows the Hausdorff dimension $D(h)$ of the set of points with Hölder singularity: $\delta A \sim \tau^h$, for a scale of τs.

Discussion

- In summary, the data show multi-fractal scaling and rare events.

P. Ivanov et al. revealed the multi-fractal scaling of beat-to-beat intervals, with only mono-fractal scaling for heart failure. This underpins the collective response in the sinus node to competing hormonal stimuli. Here, a *collective* behavior of cardiac excitable cells emerges because of high beating rates and memory effects. Physiologically, what our model crucially builds on is that slight alterations of the electrical synapse kinetics, make the network of cells undergo a transition to spatio-temporal *desynchronization*. The hypothesis is straightforwardly extending steady-state properties of connexins: voltage-gated hemi-channels are also sensitive to local electro-chemical potential gradients (third line of eq.(1)).

- The abnormal physiology may be related to *polarized* connexins.
- Alternatives are:
  - The electrotonic coupling of fibroblasts to connexins Cx43 and Cx45. This has the correct time scale of ~ 100 *ms*.
  - Ryanodine sensitive (RyR2) calcium channels of the sarcoplasmic reticulum, in excitation-contraction coupling. However the time scale is reported to be quite too small.
- The creeping of altered conduction properties throughout the tissue is a candidate description of *electrical remodeling*. Down regulation (e.g. from the accumulation of Calcium) with slower time scales would lead to long term remodeling.
- As the creeping velocity increases, *vulnerability* increases.
- Randomly driven excitatory and inhibitory couplings: is there a *glassy phase transition*, which mimics paroxysmal fibrillation to chronic?
- Critical region is very large, *Griffiths* in a broad sense. Infinite range correlations, power law tail PDFs, 1/f power spectrum, broad singularity spectrum. This is common to many models of disordered networks exhibiting avalanches, here of defects.
- Since pulses are chiral, back-scattering may be related to a *chiral anomaly* (θ term).
- With the gap junction currents, the relevant symmetries jumps from compact **U**(1) to **O**(3). Is it possible to define a critical coupling $\sim T^{-1}$, like $T^* = \frac{2\pi(D-2)}{n-2}$?
- Would this define a *sudden death critical point*?

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